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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/722,659	09/27/96	BENNETT D	I04385.140

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HOLLIE L BAKER
HALE AND DORR
1455 PENNSYLVANIA AVENUE NW
WASHINGTON DC 20004-1008

EXAMINER	
LUBET,M	
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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/722,659	Applicant(s) Bennett et al.
	Examiner Lubet	Group Art Unit 1816

☒ Responsive to communication(s) filed on *Sep 29, 1996*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17* is/are pending in the application.

Of the above, claim(s) *8, 9, 11-14, and 17* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-7, 10, 15, and 16* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This Application is related to 60/004,622, filed September 29, 1995.

2. Claims 1-17 are pending.

3. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7, 10 and 15-16 drawn to heparinase and method to decrease inflammatory response by administering heparinase classified in class 424 , subclass 96.61.

II. Claims 8,9, 11-15 and 17, drawn to fusion protein comprising heparinase and a ligand and a method to decrease inflammatory response by administering fusion protein, classified in class 424, subclass 192.1.

4. The inventions are distinct, each from the other because of the following reasons:

The inventions are distinct, each from the other because of the following reasons: Inventions and are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions . In the instant case, the Inventions I-II are materially different processes and are practiced with materially different products. They are patentable over one another. In addition, the search for one of the groups would not be expected to reveal all the references relevant to the other, and therefore the search and examination would be unduly burdensome.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated in proper.

5. Should the invention of Group II be elected, a further election of species is required and the following requirement shall apply: This application contains claims directed to the following patentably distinct species of the claimed invention:

a. fusion protein wherein in the ligand is an cytokine, antibody, intergrin and selectrin.

6. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

7. During a telephone conversation with Holly Baker on September 23, 1997, a provisional election was made to prosecute the invention of Group I, claims 1-7, 10, 15 and 16. Affirmation of this election must be made by applicant in responding to this Office action. Claims 8,9, 11-15 and 17 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claim 15 was examined as it read upon a composition comprising heparinase.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h)

9. Claims 1-7, 10, 15 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "decrease" in claim 1 and "decreases" in Claim 3 are relative terms which render these claims indefinite. The term "decrease" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.

B. The term "inhibits" in claim 5 is a relative term which renders the claim indefinite. The term "inhibits" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.

C. The term "overexpressed " in claim 6 is a relative term which renders the claim indefinite. The term "overexpressed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are unclear.

D. In claim 1, it is unclear if the heparinase is administered directly to the site of inflammation, IE topically, or systemically, IE intravenously. Does " administration" encompass systemic and topical administration?

E. It is unclear what an "heparinase enzyme" is. What enzymatic reaction does the heparinase mediate? Does the term encompass platelet heparitinase taught by Vlodavsky et al.(AB) (see page 116, in particular)? It is noted that "heparanase" is an alternative spelling for "heparinase."

10. Claim 16 provides for the use of heparinase , but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 16 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex*

parte Dunki, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

11. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to decrease inflammatory response in ischemic tissue, does not reasonably provide enablement for numerous inflammatory diseases or conditions disclosed on page 1, lines 25-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Reasons are set forth below

A. The effectiveness of treating inflammatory conditions such as organ transplantation, allograft rejection, rheumatoid arthritis, asthma, rhinitis and glomerulonephritis by administering heparinase *in vivo* is unknown.

Pharmaceutical therapies are unpredictable for the following reasons: (1) the peptide(s) or protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to inherently short half-life of the peptide or protein; (2) the peptide(s) or protein may not reach the target area, i.e. the peptide(s) or protein may not be not be able to cross the mucosa or may be adsorbed by fluids, cells and tissues where the peptide(s) or protein has no effect, (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD. APP. & Inter. 1992).

Burnham (U)(AM. J. Hospt Pharm 51: 210, 1994) teach that use of therapeutic proteins is unpredictable because the proteins have poor stability and short half-lives *in vivo* and their

repeated use leads to immunogenic response, leading to a vicious cycle of raising the dose, which enhances the immune reaction which increases clearance.

Therefore, in view of the nature of the invention, the state of the art, the amount of guidance present in the specification, and the breath of the claims, it would take undue experimentation to practice the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13. Claim 10 is rejected under 35 U.S.C. 102(a) as being anticipated by Hoogewerf et al. (W) (J. Biol. Chem 270:3268, February, 1995) or Gilat et al. (X)(J. Exp. Med. 181:1929, May, 1995) Claim 10 is directed to a pharmaceutical composition comprising a heparinase enzyme.

A. Hoogewerf et al. teach a pharmaceutical composition comprising heparanase enzyme obtained from human platelets (see abstract and page 3269, in particular).

B. Gilat et al. teach pharmaceutical composition comprising heparanase enzyme obtained from human placenta (see pages 1929-1930, in particular).

14. Claim 10 is rejected under 35 U.S.C. 102(a) as being anticipated by Vlodavsky et al.)AB) (Invasion Metastasis 12:112, 1992). Claim 10 is directed to a pharmaceutical composition comprising a heparinase enzyme.

A. Vlodavsky et al. teach a heparanase enzyme, heparitinase. The heparitinase enzyme taught by Vlodavsky et al. is encompassed by the claim language since the specification discloses on page 14, lines 19-33 that heparanase enzyme is an enzyme that degrades heparin.

15. Claims 1, 10 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Lider et al. (Y)(PNAS 92:5037, May 1995). Claims 1, 10 and 16 are directed to pharmaceutical composition of heparinase enzyme and methods of treating inflammatory responses by administering heparinase

A. Lider et al. teach a pharmaceutical composition comprising heparanase enzyme obtained from human placenta. (see page 5037, in particular). Lider et al. teach a method to decrease localized inflammatory response by administering heparinase to mice to inhibit DTH reaction to oxazolone. Lider et al. also teach that a DTH reaction is a T cell mediated inflammatory response (see page 5039 and Table 2, in particular). Lider et al. also teach that heparanase inhibits secretion of TNF α and that TNF-α is a major element in T cell mediated inflammatory responses (see page 5039, second and Table 3, and Figure 3, in particular).

16. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Zimmerman et al. US 5,169,772 (issued Dec. 8, 1992). Claim 10 is directed to a pharmaceutical composition comprising a heparinase enzyme.

A. The '772 Patent discloses heparinase enzymes expressed by *Flavobacteruim heparinum* and a method of producing heparinase enzyme recombinantly in an organism in which it does not naturally occur (see column 3, line 26 through column 6, line 16, and column 8 line 4 through column 10 and claims 1-2, in particular).

17. Claim 10 is rejected Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by as being anticipated by Fuks et al. US Patent 5,362,641 (issued Nov. 8, 1994, filed March 7, 1991). Claim 10 is directed to a pharmaceutical composition comprising a heparinase enzyme.

A. The '641 Patent discloses purified heparanase obtained from human SK-HEP-1 in pharmaceutical composition (see column 12, line 59 through column 16, line 54 and claims 1-39, in particular). The '641 Patent further teaches that FGF is released by addition of heparanase to extracellular matrix (ECM) which promotes wound healing. The '641 Patent also discloses but does not exemplify that administration of heparanase can be used to treat diseases or conditions such as transplantation, diabetes, hypertension, cerebral and peripheral ischaemic disease, and diseases associated with vascular damage, such as diabetes, hypertension and systemic lupus erythematosus (see column 4, line 38 through column 5, line 6, in particular).

18. Claims 10 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Sasisekharan et al. US Patent 5,567,417 (issued October 22, 1996 and has priority to November 17, 1993) .

Claim 10 is directed to a pharmaceutical composition comprising a heparinase enzyme. Claim 15 is directed to a pharmaceutical composition of heparinase enzyme in carriers such as liposomes and biogregradable polymeric matrices.

A. The '417 Patent discloses pharmaceutical compositions for delivering an effective dose of heparinase (see column 8, line 29 through column 11, line 7 and Claims 1 in particular). The '417 Patent also discloses that the heparinase may be administered in composition comprising biodegradable polymeric matrices or liposomes (see Claims 4 and 8, column 16, lines 17-27, in particular). The '417 Patent discloses three heparin enzymes produced by Flavobacterium heparinum. The '417 Patent further discloses that Heparinases I and II inhibits both neovascularization *in vivo* and proliferation of capillary endothelial cells mediated by fibroblast growth factor in vitro. The '417 Patent also teaches that Heparinase II did not inhibit neovascularization *in vivo*, l but is useful in the alteration of smooth muscle cell proliferation (see column 3, line 33 through column 4, line 39, in particular). The '417 Patent further discloses but does not exemplify the use of heparinase to treat disease in which neovascularization plays a prominent role such as rheumatoid arthritis and eye diseases such as diabetic retinopathy, neovascular glaucoma, and inflammatory eye disease (see column 1, line 47 through column 2, line 25, in particular).

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 10 and 15 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogewerf et al. (W) (J. Biol. Chem 270:3268, February, 1995) or Gilat et al. (X)(J. Exp. Med. 181:1929, May, 1995), Vlodavsky et al (AA) (Invasion Metastasis 12: 112, 1991), Lider et al. (Y)(PNAS 92:5037, May 1995) Zimmerman et al. US 5,169,772 (issued Dec. 8, 1992) Fuks et al. US Patent 5,362,641 (issued Nov. 8, 1994, filed March 7, 1991) and Sasisekharan et al. US Patent 5,567,417 (issued October 22, 1996 has priority to November 17, 1993). The claims are directed to compositions comprising heparinase enzymes in carriers such as liposomes, lipoospheres, proteosomes, microspheres, microcapsules or biodegradable polymeric matrices.

A. Hoogewerf et al. Gilat et al. Vlodavsky et al., Lider et al. , the '772 , the '641 and the '417 have been discussed supra. These references all teach pharmaceutical compositions of heparinase enzymes.

B. Hoogewerf et al., Gilat et al, Vlodavsky et al., Lider et al., '772 and the '641 Patents do not teach compositions comprising heparinase and carriers for administration of heparinase enzymes wherein the carrier is liposomes, lipoospheres, proteosomes, microspheres, microcapsules or biodegradable polymeric matrices. However of the use of carriers recited in Claim 15 to administer proteins is well known in the art as is acknowledged by the instant specification on page 22, line 20 through page 23, line 36 and the '417 Patent. Therefore, it would have been obvious to one with skill in the art at the time of the invention to formulate the heparanases taught

by Hoogewerf et al. Gilat et al., Lider et al. , the '772 , the '641 and the '417 in any of the carriers recited in Claim 15.

21. Claims 1- 7, 10, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogewerf et al. (W) (J. Biol. Chem 270:3268, February, 1995) or Gilat et al. (X)(J. Exp. Med. 181:1929, May, 1995), Vlodavsky et al (AB) (Invasion Metastasis 12: 112, 1991), Lider et al. (Y)(PNAS 92:5037, May 1995) Zimmerman et al. US 5,169,772 (issued Dec. 8, 1992) Fuks et al. US Patent 5,362,641 (issued Nov. 8, 1994, filed March 7, 1991) and Sasisekharan et al. US Patent 5,567,417 (issued October 22, 1996 has priority to November 17, 1993) in view of Ratner et al. (Invasion Metastasis 12:82, 1992).. or Gilat et al(AA) (J. Immunol. 153: 4899, 1994). The claims are directed to methods of treating localized inflammatory responses by administering heparinase enzymes.

A. Hoogewerf et al. Gilat et al. Vlodavsky et al., Lider et al. , the '772 , the '641 and the '417 Patent have been discussed supra. These references all teach pharmaceutical compositions of heparinase enzymes.

B. Hoogewerf et al., Gilat et al, , Vlodavsky et al. and the '772 Patent do not teach the use of the heparinase enzymes to treat inflammatory responses or that heparinase enzyme decreases accumulation of leukocytes or inhibits leukocyte extravasation. However, the limitations recited in Claims 2-5 are inherent properties of the heparinase enzymes. Ratner et al. teach that heparanases digests heparin and heparin sulfate from endothelial cell surfaces and facilitates T cell movement through the basement membranes (see page 82, in particular). Gilat et al.(AA) teach

that heparanases degrades heparin from ECM which leads to the release of cytokines which leads to lymphocytes becoming mobile and migrating to adjacent sites of inflammation.

As summarized supra, Lider et al teach that heparanase inhibits secretion of TNFα and that TNFα is a major mediator in T cell mediated inflammatory responses. The '641 and '417 Patents disclose but do not exemplify administration of heparanases to treat localized inflammatory responses in a variety of diseases including cerebral and peripheral ischaemic disease, diabetes, systemic lupus, inflammatory eye disease and rheumatoid arthritis.

Therefore it would have been obvious to one with skill in the art to administer heparinase enzymes taught by Hoogewerf et al., Gilat et al., Vlodavsky et al., Lider et al. and the '772 , the '641 and the '417 Patents with the expectation that inflammatory responses would be decreased as taught by Lider et al. and the '641 and '417 Patents.

22. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 10, 15 and 16 are provisionally rejected under the judicially created doctrine of obvious- type double patenting over claims 1-10 of copending Application No. 08/273,109.Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of 08/273,109 pertain to method of treating wounds by administering heparinase. Wound healing is a type of inflammatory response, since inflammatory cells, such as neutrophils, participate in wound healing and many of the "inflammatory cytokines" IE TNF-α are participate in wound healing.

23. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

24 Any inquiry concerning this communication or earlier communications from the examiner should be directed to Martha Lubet whose telephone number is (703) 305-7148. The examiner can normally be reached on Monday through Friday from 8:15 AM to 4:45 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for this group is (703) 305-3014 or 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Martha Lubet

September 26, 1997

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800